SUPPORT AND MANAGEMENT FOR THE PROJECT:
"EFFECTS OF THE CHERNOBYL ACCIDENT ON THYROID CANCER AND LEUKEMIA/LYMPHOMA"
CONTRACT BETWEEN NATIONAL CANCER INSTITUTE AND THE TRUSTEES OF
COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK
YEAR THREE ANNUAL REPORT AND SUMMARY OF BASE PERIOD OF THE CONTRACT
SEPTEMBER 30, 1997 - SEPTEMBER 29, 2000

1. Introduction

This report summarizes work carried out, and progress to date, under the above contract between the National Cancer Institute (NCI) and Columbia University, which provides scientific and administrative support for three studies of the health consequences of the Chernobyl accident. This report serves as the annual report for October 1999-September 2000, as required under the contract, but in addition to covering this period, it also summarizes work carried out during the entire three years given that the base period of the contract is now complete.

The Request for Proposals (RFP) with respect to the contract (RFP #2-CB-77032-08), was issued by NCI on March 7, 1997, Columbia submitted an application in response to the RFP, and was awarded the contract in September 1997. The contract came into effect on September 30, 1997, and the base period of the contract expired on September 29, 2000.

Initially, the contract supported, or partially supported, a number of scientists/clinicians and administrative staff from Columbia. In addition, a subcontract with the University of Utah provided dosimetric expertise. During the evolution of the contract, adjustments were made in staffing requirements to more realistically reflect needs. Appendix 1 lists the Columbia scientific and administrative staff together with collaborators from other institutions who have been involved at some time during the first three years of the contract. NCI had several individuals acting as consultants to the various studies, and these consultants became consultants to Columbia (primarily for administrative reasons) on March 30, 1999. These consultants are also listed in Appendix 1.

NCI requested that Columbia take responsibility for the purchases of supplies and equipment on March 30, 1999, a task which was not envisaged under the original contract. This has been implemented, in addition to several other extra administrative activities, including responsibility for travel, and subcontracts with the University of Illinois for data processing services in Ukraine, and the Clinical Research Institute of Radiation Medicine and Endocrinology in Belarus for financial support of the study. These activities are described in more detail below (see Section 4).

The primary areas in which Columbia personnel have worked are epidemiology and data management, clinical and laboratory activities, dosimetry and administration. The activities which have been carried out in these various areas (except administration) are described in the following sections with regard to the three studies which are included under the contract. Detailed quarterly reports have been provided to NCI throughout the three years and this report provides an overall summary of progress and achievements to date. In some disciplinary areas these summaries are, in effect, summaries of progress in the studies themselves, since Columbia investigators are intimately involved in all aspects of the studies in these areas. No attempt is made to separate the contributions of Columbia staff, Columbia consultants, NCI staff and others since the work is closely integrated; as stated, more specific details of the particular role of Columbia staff has been provided in previously submitted quarterly reports. In the areas of dosimetry and administration, the work has been much more specifically task oriented, and thus the report covering these areas covers only activities performed by Columbia or their subcontractors.

2. Studies of Thyroid Cancer

2.1 Introduction:

Two cohort studies are being conducted, one in Belarus, the other in Ukraine. The cohorts consist of individuals who were between the ages of 0 and 18 years at the time of the Chernobyl accident, and were exposed to radioactive fallout, primarily from various iodine isotopes, most notably I^{131}. The activity of the thyroid gland was measured instrumentally in all study subjects shortly after the time of the accident. Current addresses for study subjects were found through a variety of sources

and subjects were then invited to participate in a screening examination for thyroid disease. The screening examination consists of ultrasonography, physical examination by an endocrinologist, various laboratory tests and interview data. The screening examinations are done at fixed centers in Minsk (Belarus) and Kiev (Ukraine) and, more recently, a fixed center in Gomel (Belarus). In addition, both countries have mobile teams which conduct such screening examinations in the field.

The plan is to repeat the screening examinations every two years for a number of cycles. The number of cycles has not yet been finally established, but it appears as though a total of five such screenings may be adequate.

The objective of the study is to relate individual thyroid dose estimates (based primarily on the activity measurements) with risk of thyroid cancer and other thyroid diseases. Unlike the substantial data on risk of thyroid cancer from external low LET radiation, data on the effect of I^{131} and other radioactive iodine isotopes are very limited. The large increase in thyroid cancer seen in Belarus and Ukraine during the past decade suggests a major contribution from such radiation exposure, but it is difficult to separate the effects of radiation from the effects of the very substantial increase in screening during the same period. By routinely screening study subjects under carefully controlled conditions, it is hoped to minimize or eliminate the potential confounding effect of screening.

2.2 Progress in Epidemiology and Data Management:

Since the original protocol for this study was prepared some years ago, a substantial modification has been made in the target size for the study cohort. Activity estimates were originally available for 38,198 measurements in Belarus, and 75,349 measurements in Ukraine. The number of people involved is slightly less due to some duplication and repeat measurements. Following a careful re-examination of the potential power of the studies, including taking measurement error in dosimetry into account, a target cohort size of 12,000 for each country has now been accepted. This study size should provide adequate power to test for a main effect of radioactive iodines on thyroid cancer risk, and an adequate power to detect a difference in the relative biological effectiveness of radioactive

iodines compared to external low LET radiation if the ratio of the RBEs is about 2:3, the value suggested by the BEIR V Committee of the National Academy of Sciences (NRC National Research Council. Committee on the Biological Effects of Ionizing Radiations, Health Effects of Exposure to Low Levels of Ionizing Radiation (BEIR V). National Academy Press, Washington, DC, 1990.). The latter assumes values for the other parameters in the power model such as the incidence of thyroid cancer in the absence of radiation, the degree of measurement error in dosimetry, etc. The power for other end points, i.e, other thyroid diseases, should be as good as or better than that for thyroid cancer given their greater incidence/prevalence rates.

In order to achieve the targets of 12,000 subjects in each country, given the location rate for potential study subjects and their participation rate, it has proved necessary to target all potential subjects in Belarus and some 34,000 potential study subjects in Ukraine. This has been done in several waves, to facilitate logistics. The sample chosen for Ukraine is stratified by the preliminary estimate of dose, but otherwise is a random sample. The stratification on dose was chosen so as to produce approximately equal numbers of expected cases within three dose categories in order to maximize power whilst at the same time permitting stable estimates in all three dose categories, to allow a meaningful evaluation for the existence of a dose response relationship.

A concern in the study was the possibility of selection bias. The location rate for potential study subjects has been less than 70% in both countries, reflecting the difficulty of tracing individuals from limited identifying information available in 1986. However, the location rate does not vary greatly by dose, and there appears to be no obvious reason why the tracing rate should be related to the risk of thyroid disease. A greater concern, therefore, is the participation rate among those traced. Initially, this was low in both countries. After careful consideration and field evaluation, a number of strategies were developed to improve participation rates and were introduced. The most successful technique appears to be providing the sum of $5 to cover the travel and inconvenience costs incurred by study subjects attending for screening. To date, this has only been possible to apply directly in Ukraine, but an analogous strategy is being developed in Belarus, although it may

not be possible to provide cash payments, but rather its equivalence in goods. Other strategies include the development of better educational material for study subjects, and increased training of recruitment staff. With these approaches the participation rate is now over 70% in Ukraine, and 44% in Belarus. Although this reduces the concern about possible selection bias, this is an issue which must remain under active consideration.

It is anticipated that the first round of screening will essentially be complete in Ukraine by the end of 2000, and in Belarus by spring 2001. Both countries should have enrolled 12,000 or more study subjects. Plans have been developed for rescreening cycles including questionnaire modifications, processes for reinviting study participants and keeping in touch with participants in intervening periods.

With regard to data management, which has primarily been the responsibility of the epidemiologists, in Ukraine a satisfactory relationship has been established with the data processing group operated through the University of Illinois in Kiev. This group carries out data entry, checking and editing of the various forms, and returns the data to the data base in the Institute of Endocrinology which is maintained by data management staff of the Institute. Responsibility for keeping track of the cohort itself is also a function of the latter data base and data management team.

In addition to the above system for data processing, the overall data management structure in Kiev has been substantially revised and modified in order to keep better track of the flow, storage and retrieval of forms. Although this has been implemented, there still needs to be an increase in timeliness of the completion and data processing of several forms, in particular, those relating to various diagnostic procedures.

The data mangement system for the Belarussian thyroid study was developed early by personnel based at the Institute of Endocrinology in Minsk. Although this system has functioned, there remains a great deal of work to do in terms of rationalization, system organization and quality

control of the data base, and this remains an urgent task.

2.3 Progress in Endocrinology:

Since the start of the contract, considerable progress has been made to minimize bias in the selection of patients for fine-needle aspiration (FNA) of thyroid nodules, in the selection of patients for surgery, and in the approach to patients with non-operated nodules. A standardized means to describe goiter size, based upon the latest WHO criteria, has been implemented in both countries and criteria for the diagnosis of autoimmune thyroiditis (AIT) have been established. Quality assurance of clinical procedures has been nurtured and extension of the screening operations to Gomel supervised. Three abstracts (Appendix 2), including two that will be presented at the International Thyroid Congress in Kyoto, have been written.

The use of consistent clinical criteria uniformly applied will lead to a more standardized management of the cohorts in Belarus and Ukraine and make it easier to integrate results from the two arms of the study. Especially important have been the criteria for performing FNA (Appendix 3), which were worked out in large part during discussions with the Belarusian group. After some initial reluctance, the Ukrainians accepted these recommendations, which will be incorporated into the two Operations Manuals. The criteria for diagnosing autoimmune thyroiditis (AIT) (Appendix 4) will be discussed at the Tri-National Meeting in November 2000 before adoption and addition to the Manuals. During the second screening cycle, the new WHO classification of goiter grades (0=no enlargement; 1=enlarged thyroid, not visible; 3=enlarged thyroid, visible with neck in neutral position) will be employed in both cohorts.

Clinical management of non-operated thyroid nodules has been discussed in the context of the need to prevent ascertainment bias by having a comparable approach in the two cohorts. Provisional methods have been developed after consultation with the Belarussians (Appendix 5). Since thyroxine therapy, which is currently not regulated, may influence the development of both benign and malignant nodules, its use should be carefully followed. Although therapy might not be identical in

the two countries, there is enough common ground to expect that it will be very similar.

2.4 Progress in Cytology/Pathology:

The Chernobyl thyroid project has made a great deal of progress in the areas of cytology and pathology over the first three years:

Sonographers performing fine needle aspiration (FNA) biopsies on nodules detected by palpation and/or ultrasound are recording the size and location of the nodules for entry into the database. The Cytology laboratory receives the sonographers' information and records the findings for entry into the database. Parallel forms for recording the cytology findings from thyroid nodule FNAs in the two participating countries, Belarus and Ukraine, have been created.

The terminology by which the diagnostic categories are designated has been defined in writing through a collaborative effort. The operations manual details the method by which FNAs are performed and reported. Results have been entered into the database in Belarus, and are in the process of being entered in Ukraine.

Despite these achievements, however, a number of further objectives will have to be met during second and subsequent screenings.

Older cases originally reviewed using the preliminary terminology will have to be transferred to the new forms and review of original cytologic slides will have to be performed whenever necessary. Staining procedures and slide preservation in the Minsk Dispensary in Belarus will have to be improved.

A system of image archiving for FNA cytologic specimens should be instituted. This will involve the purchase of a digitized CCD camera and a computerized image collection and storage system.

Improved adequacy of FNA specimens in Belarus is urgent. This will involve: additional training for sonographers; more needle sticks per case; limiting the performance of FNAs to those with credentials to perform the procedure based on their adequacy rates; instituting immediate assessment of adequacy of FNA specimens in Minsk, Aksakovshina and Dr. Dmidchik's Oncopathology Center as soon as possible; purchasing at least one new microscope and additional lens for anexisting microscope; and training cytologists and sonographers to perform immediate assessment.

In Kiev, timely completion of cytology forms and access to forms for slide review needs to be improved.

Continued FNA slide review by expert cytopathologist and histology slide review by an International Panel with cytologist monitoring specimen adequacy, diagnostic reliability, and laboratory quality (i.e.,staining procedures) is essential.

2.5 Progress in Ultrasonography:

Ultrasounnd systems were maintained in operational circumstances, and the rate of study conduct was not limited by ultrasound resources. New light weight good quality ultrasound machines were identified and used for field studies (GE alpha systems which are also used by the Sasakawa project in Gomel).

New general purpose computer-based ultrasound image recording devices were developed by staff at the Belarus Academy of Sciences, and tested for one year in the Minsk Dispensary. Based on the quality of the data, and the likely robustness of the system it was decided to acquire the same system for use in fixed and field installations.

The ultrasonographers are all physicians trained in endocrinology and in the use of ultrasound instruments and they are highly skilled workers. Ultrasound guided fine needle aspiration biopsies are performed in the fixed centers, and the procedures are technically performed with excellent

patient response. Patients with abnormal and suspicious findings (nodules exceeding a 5-10 mm size) are biopsied and followed vigorously.

Some problems have, however, been encountered during the past three years. There have been equipment failures in Belarus with the ultrasound recording systems which were repaired by swapping MOD disk drives after the drive failed. When it failed a second time, U.S. collaborators were not informed for about half a year, so there was a lapse in data archiving. Spare recording devices were acquired for Ukraine, but not for Belarus. Systems taken to the field in Belarus did not have digital recording equipment, while in the past year data recording was done in the field using MOD drives attached to portable ultrasound devices which were transferred from an OB project to the present project. Thus, only a small fraction of field studies have digitally archived data.

The relatively high cost of ultrasound equipment held back the purchase of needed portable ultrasound units, adequate numbers of archiving systems, and test phantoms for taking to the field.

Fine needle aspiration studies are not done in the field, and it has been difficult to get patients with suspicious findings into the large centers or to Aksokovchina for follow-up (initial biopsy or repeats when samples were inadequate).

A quality control review of the clinical images has not been developed, and it is not clear how that review should be conducted. There are technical and logistic issues that need to be solved.

2.6 Progress in Laboratory Investigations:

Since the onset of the project, there have been four major areas of activity related to laboratory operations: selection of the proper instrumentation and test methods, assessment of tests to be performed, introduction and review of Quality Control procedures, and management of supplies.

Testing began in the BelAM project before testing started in the UkrAM project. Initially, Dr.

Petrenko's Central Laboratory in Minsk used a Chiron analyzer for Ionized Calcium, an Abbott IMX immunoassay for TSH, and radioimmunoassay methods for TG, anti-TPO, anti-TG, free T4, and PTH. In Kyiv, Dr. Epshtein planned to use the same Chiron analyzer for Ionized Calcium, a different method (chemiluminescent) for TSH, free T4, TG, and anti-TPO, and radioimmunoassay for PTH. It was clear that having both projects use the same methods would facilitate the monitoring of testing and the comparison of results. Nonetheless, this recommendation was ignored until problems in acquiring Abbott reagents, problems with the short shelf life of RIA test kits, and problems with maintaining equipment led the BelAM project to adopt the same chemiluminescent test methods as in Ukraine. Thus, at present, both laboratories are using the same test methods and should continue to do so over the course of the project.

From the start of the studies, there has been discussion over the need to perform TG, anti-TG, and urinary iodine on every patient for each screening cycle. In the BelAM project, TG and anti-TG were to be performed on every patient in the first screening cycle; in the UkrAM project, only TG was to be performed because the Ukrainians did not consider anti-TG useful. As the project has proceeded, the available TG data seems to support the view that this test should not be performed beyond the first screening cycle. In contrast, a review of the available Belarussian anti-TG data suggests that this test should be added to the UkrAM protocol. These recommendations were discussed at the Clinical meeting in September 2000, and will be finalized when all the first cycle data are available.

Additionally, there has been considerable controversy over the need for urinary iodine testing. The BelAM protocol called for performing a random urinary iodine test on all patients for the first screening cycle; the UkrAM protocol called for performing the test on only a sample of patients for the first screening cycle, but in practice, the test has been performed on every patient. Both countries seem interested in continuing these measurements although the utility is uncertain. The Ukrainians, in particular, are interested because of Dr. Kravchenko's research interest in iodine nutrition that precedes this project. Of note is that the state of iodine nutrition is changing in both countries. The

reported usage of iodized salt or iodine supplements, as reported by the Belarussian cohort, has risen from 15% to near 50% over the course of the project. Very low levels of usage in Ukraine will rise soon as a government program mandating iodination of salt begins in the next year or two.

However, the validity of a random urinary iodine measurement and the applicability of the data, even if accurate, has been discussed on several occasions. It is felt that the state of iodine nutrition might affect the development of cancer and/or thyroiditis. Thus, changing usage patterns may need to be tracked during the study. On the other hand, it may be that only the iodine status at the time of the accident is relevant. The uncertain nature of this controversy led to the scheduling of an Iodine Nutritional Workshop in Bethesda during the 2000 tri-national meeting. This workshop will bring in outside experts to help assess this issue.

Quality control has been another key area of activity. Prior to the initiation of this project, the Belarussians and Ukrainians did not have well developed laboratory quality control programs. Quality Control consisted of running repeat high and/or low specimens with each analytical run with no statistical analysis of the results. Introducing modern quality control procedures was an initial objective. After the orientation visit in February, 1998, the next two or three visits were spent explaining statistical quality control to the laboratory directors and their staffs; literature and graphical examples were given to the laboratory directors. Subsequent visits were spent reviewing and discussing the implementation of these procedures. The laboratory directors seem committed to the quality control program and the quality control data have proven useful in detecting analytical problems. Nonetheless, there have been problems with the way the laboratories respond to out-of-control situations. Ongoing objectives are to improve their implementation of quality control procedures and to continue monitoring analytical quality.

Finally, considerable effort has been expended in trying to establish a smoothly running system for providing supplies to the laboratories and screening centers. Both the Ukrainians and Belarussians were repeatedly running out of supplies. The major problems seemed to be payment difficulties and

a failure to anticipate requirements. Since the purchase and shipment of these supplies has become a Columbia University responsibility, the situation has improved. Payment problems have been resolved and an understanding of the ongoing requirements has been gained during the first ordering cycle. In addition, an inventory reporting form was introduced for the laboratory in Belarus to track utilization more closely; this form seems to be helping. Future objectives are to refine this form and introduce a similar system into Ukraine.

2.7 ^{129}I Dosimetry:

A major difficulty in the reconstruction of dose to the thyroid is the unavailability of reliable measurements of radioiodine in some regions where the incidence of thyroid cancer is in fact substantial. The reason for the lack of radioiodine data is the short half life of the iodine isotope that produced most of the thyroid dose, i.e., ^{131}I (half life, 8.04 d). Adequate data were unfortunately not collected immediately after the accident on the intensities and patterns of ^{131}I-deposition density.

In order to overcome this limitation, a feasibility study supported by DOE (Dr. Straume, PI) was conducted to determine whether the long lived ^{129}I isotope (half life, 16 x 10^6 y) could be used today to reconstruct ^{131}I-deposition densities and thus help in the thyroid-dosimetry effort. The feasibility study involved a soil-sampling expedition in Belarus in 1993 where samples were systematically collected according to a ^{137}Cs-deposition gradient from the relatively uncontaminated Vitebsk region in northeastern Belarus to within 30 km of Chernobyl. The samples were 30-cm deep cores of soil that were cut into seven depth layers. Each layer was then measured by gamma spectrometry for ^{137}Cs and subsequently analyzed for total iodine concentration using gas chromatography and ^{129}I using AMS.

Results from the feasibility study demonstrated that (1) the deposition density of ^{129}I from the Chernobyl accident can be accurately reconstructed now (and in the foreseeable future) using AMS to measure ^{129}I in soil cores, (2) cesium does not appear to be an adequate surrogate for iodine deposition (^{129}I -to-^{137}Cs ratios vary by more than a factor of 20), and (3) the ^{129}I -to-^{131}I ratio appears

appears to be constant and thus should provide a reliable means to scale from contemporary ^{129}I measurements to the initial levels of ^{131}I. Additional measurements of ^{129}I should be performed on archived soil samples in order to solidify the data on ^{129}I to-^{131}I ratios.

More recently, the DOE has undertaken a larger study (Dr. Straume, PI) to measure deposition of ^{129} and total iodine concentrations in soil for the entire country of Belarus. This study was initiated in January 1997 and was completed in 2000. The successful completion of this study benefited significantly from the synergism provided by the present effort. Results from this study will prove very valuable for the present NCI effort to reconstruct thyroid doses in Belarus, especially for those regions where little or no direct thyroid measurements were made.

This project has assisted the NCI thyroid dose reconstruction effort and worked closely with participating scientists in Belarus. Also, we worked closely with the DOE funded ^{129}I Dosimetry project in Belarus to coordinate efforts. We also assisted in study designs, in the use of appropriate laboratory methods, in the recommendation of ^{129}I measurement facilities in the US, in the interpretation of results, in quality control, and in the recommendation of improved methods as they became available. Because the DOE study to measure ^{129}I deposition in Belarus was rather coarse by design, i.e., only a few sampling sites per region, it is likely that additional soil samples will be required in the future to focus in on certain locations of particular importance to the NCI effort.

The results from this study was presented in Straume et al. *^{129}I Dosimetry: A Demonstration Project for the Use of ^{129}I as a Surrogate for ^{131}I in Belarus and Other Regions Contaminated by Chernobyl Fallout*, Final Report to DOE/EH-63 (February 18, 2000). The following conclusions was drawn from the available iodine soil data:

- Both ^{129}I and ^{137}Cs are retained firmly in the top ~15 to 20 cm of the soil and thus the possibility for obtaining samples for deposition-density measurements will remain.
- Deposition densities of ^{129}I can be measured accurately using the methods and AMS capabilities

developed under the Feasibility Study (e.g., Straume et al. 1996, Marchetti et al. 1997) and the present Follow-on Study.

- The results show good agreement between ^{131}I deposition inferred from our ^{129}I measurements and ^{131}I actually measured in the same settlements in 1986.
- In contrast, the correlation between ^{129}I and ^{137}Cs deposition is poor, hence ^{137}Cs is not a reliable surrogate for ^{131}I.
- Indications are that total iodine concentrations in top soil from Belarus are low compared with other regions of the world where radiogenic thyroid cancer has been studied (e.g., Japan and Marshall Islands, where iodine is obtained from sea food diets as well). This suggests the need for additional evaluations to explore whether the relatively low iodine concentrations in Belarus soil resulted in low concentrations in the diet and whether this might have modified the risk of developing radiogenic thyroid cancer.
- Finally, the use of ^{129}I deposition data measured by AMS appears to be the only method currently available to obtain reliable radioiodine deposition densities in regions where direct iodine measurements were absent or inadequate and, also, to provide confirmation and QC in areas where such measurements were made.

3. Study of Leukemia

3.1 Introduction:

The leukemia study being carried out in Ukraine is a case-control study conducted within a cohort of approximately 100,000 clean up workers, who first worked in the 30 km zone between 1986 and 1991. The primary objective is to estimate the risk of leukemia as a function of individual bone marrow dose, and other modifying factors such as age at exposure and time since exposure. In particular, two primary hypotheses will be tested, namely, that there is no increase in risk of leukemia, and secondly, if there is such an increase in risk, the magnitude of the risk will be less than that observed in high-dose high-dose rate studies such as the atomic bomb survivors. These hypotheses are of particular interest since doses received by the liquidators were generally highly fractionated and at relatively moderate dose rates, and thus are more analogous to contemporary

situations of interest. Other target diseases of interest in addition to leukemia are multiple myeloma and myelodysplasia with similar objectives.

The cohort is being identified through the Chernobyl State Registry and consists of clean up workers resident at the time of registration in one of five oblasts, or Kiev City. Cases of leukemia, myelodysplasia or multiple myeloma are being identified by forming a "Leukemia Registry" from all available records in the study area, then linking the cohort to the leukemia registry using probablistic record linkage. Interviews will then be sought with all relevant cases, and a set of 5:1 matched controls. The primary purpose of the interview is to ascertain information relevant to estimating individual bone marrow doses, and also any potential confounding factors. A detailed pathological and medical record review will be conducted of all cases identified among the clean up workers to confirm the accuracy of their original diagnosis. The study is being carried out in collaboration with the Research Center for Radiation Medicine in Kiev, and the Ukrainian study director is Professor A.Y. Romanenko.

During the three years of the present contract, work has primarily focused on conducting a feasibility (Phase I) study to assess feasibility, and to develop appropriate study methods. The Phase I study was completed and a report prepared at the end of 1999. A full study proposal was prepared early in 2000, and following assessment by various NCI groups, it was decided to proceed with the full study. Various preparatory tasks were completed by September 2000, and the full study initiated as of October 2000. It is estimated that the study will require four years to completion.

3.2 Progress in Epidemiology and Data Management:

During the three years of the contract various tasks have been accomplished in epidemiology. For convenience, these are divided into those during the Phase I study (to the end of 1999) and those completed since. These tasks are summarized below in point form:

Phase I Study:

A. The Chernobyl State Registry was investigated to determine its provenance, its information content and the feasibility of accessing the Registry.

B. A potential cohort for the Phase II study was obtained from the Registry. The characteristics of the cohort were investigated, such as availability of official doses, available for about 47% of the cohort.

C. An investigation was carried out to determine the feasibility of tracing cohort members. This was done by means of a pilot study in the oblast of Dnipropetrovsk. It was determined for this oblast that 90% of clean up workers had a medical examination within the past three years, as recorded on the Registry. Of the remaining 10%, more than half could be found from other sources.

D. A sample of 47 liquidators was chosen, and invited to come to the Medical Center for interviewing. The response rate was approximately 66%.

E. The feasibility of using the existing dosimetric questionnaire was tested on those subjects who responded to the invitation as above.

F. Blood draws were carried out on a small number of subjects who were interviewed. This was to test the feasibility of obtaining blood if, for example, FISH dosimetry was to be used in the full study.

G. The epidemiologists also assisted in the conduct of the diagnostic review (described below) to evaluate the quality and availability of diagnostic material in Ukraine.

Interim Period

During the interim period a number of tasks were completed which involved epidemiologists, often in conjunction with dosimetrists and hematologists. In summary, these tasks are:

A. The identification, recruitment and training for the individual oblast study teams (hematologists, supervisor, research assistant/interviewer).

B. The development of the study operations manual.

C. The establishment of the data management system for the study.

D. A detailed survey in each oblast of sources for case ascertainment, i.e., the source from which the leukemia registry will be compiled. This assessment included identifying appropriate sources of records, the content of these records and, as far as possible, their completeness. This, of course, formed the basis for the methods to be used to develop a leukemia registry.
E. Discussions were conducted with the Ministry of Internal Affairs to seek access to their liquidator files.
F. The oblasts to be included in the study were coonfirmed and the cohort database was established.
G. Interviews were completed with approximately 50 liquidators for whom teeth were available for EPR.

3.3 Progress in Hematology:

Early investigation of the hematology and pathology departments of several hospitals in Dnipropetrovsk oblast indicated that medical records, bone marrow smears and tissue sections from many patients with either leukemia or lymphoma had been retained in a reasonable state of preservation from 8-10 years or more. The hospital administrators and oblast hematologists expressed their willingness to cooperate with the proposed project and to make available the medical records and tissues of patients with these disorders for diagnostic review in Kiev, as proposed in the protocol of the study.

Many discussions were held with many of the hematologists and administrators of the major hospitals of the oblasts which were targeted for the Phase II study over the two year period of Phase I concerning the objectives and procedures necessary for completion of the project. Six meetings were held with the responsible personnel in the oblast of Dnipropetrovsk. It was concluded from these meetings that cooperation for the proposed study would be excellent.

In the fall of 1998 a team of epidemiologists and hematologists from the Research Center for Radiation Medicine (RCRM) visited the major hospitals in Kiev City and 5 oblasts for the purpose of identifying and sending to Kiev the bone marrow slides and abstracted medical records from cases

of leukemia, lymphoma and related hematological disorders for review by an international panel of expert hematologists. The primary purpose of the review was to determine the extent to which the diagnosis of a representative group of randomly selected cases of leukemia and related disorders in the hospitals targeted for eventual inclusion in a Phase II study could be confirmed by the panel of expert hematologists. Other objectives were to determine the availability of histologic materials and medical records, their quality and the extent to which the classification of the various types of leukemia and lymphoma could be verified. The bone marrow slides and medical records for 20 cases of 8 specific hematological disorders were requested to be randomly selected from males, ages 20-60, in the general population of each oblast, with disease which occurred between the years 1987 and 1998, divided as equitably as possible into three separate time periods. The eventual review of 115 cases of leukemia, lymphoma and related disorders which was held in Kiev during the week of January 18, 1999 concluded that the rates for histologic confirmation of disease and types of disease for the original diagnoses of leukemia cases were in the range of 90% or greater. Disease confirmation rates for lymphoma were similar. The quality of the bone marrow slides generally was quite satisfactory. The study also indicated that the rates of confirmation for cases of myelodysplasia and multiple myeloma were quite good but that it was virtually impossible to confirm the diagnosis of many types of refractory anemia due to the absence of bone marrow biopsy materials. Other information learned from the study was that the recovery of medical records and bone marrow slides for the early years following the Chernobyl accident were much lower than those for the more recent years and that very little histological material could be recovered from two targeted oblasts due to the occurrence of local disasters. In virtually all oblasts the recovery of medical records was better than that for bone marrow slides. Later studies conducted in four oblasts indicated that the recovery of medical records and bone marrow slides for Chernobyl clean-up workers reported to have leukemia is considerably higher than for their surrogate population of males in the general population in several of the oblasts. The most important conclusion from the two studies was that the prospect is excellent for confirmation of retrospective cases of leukemia and several related hematological disorders in Chernobyl clean-up workers through the evaluation of medical records and bone marrow slides of suitable regions in Ukraine.

The hematology records of the hematology department of hospital #4 in Dnipropetrovsk were searched for cases of leukemia-related disorders which occurred during the years 1987, 1993 and 1998. The results indicated that myelodysplasia was recognized as early as 1987 and that the cases were included as such in the hospital list of cases. Only one patient with a leukemia-related disorder was identified as a clean-up worker and he was not listed in the State Registry.

Pre-treatment peripheral blood bone marrow and/or other tissues from 25 clean-up workers with leukemia or a related disorder were cryopreserved. Similarly, aliquots of pretreatment peripheral blood from several patients with leukemia were sent to RCRM for isolation and cryopreservation of malignant cells for possible future molecular studies. Ten clean-up workers with leukemia and other hematological disorders were studied by means of G-banding cytogenetics. Aliquots of peripheral blood from 20 clean-up workers in a single oblast were sent to RCRM where their mononuclear cells were isolated and cryopreserved in anticipation of future radiation dose estimation by means of FISH biodosimetry. Preparations also were made for the future immunophenotyping of lymphoma tissue slides. About 1800 clean-up workers with radiation dose estimates of 500 mGy or greater were identified by means of referrals to RCRM and through various hematology clinics. Peripheral blood mononuclear cells and bone marrow from several of these individuals were cryopreserved in anticipation of possibly conducting future molecular biological and biological dosimetry comparison studies on as many of these persons as is possible.

The hematologists have also been heavily involved in plans for the leukemia registry. In particular, there have been information sessions with hematologists from the various study areas, and a detailed list of diagnoses to be included in the leukemia registry has been drawn up.

3.4 Dosimetry EPR:

Support in the area of Electron Magnetic Resonance (EPR) dosimetry was provided by the University of Utah under subcontract with Columbia University. The support involved assessment and validation of the accuracy obtainable with EPR techniques.

Dr. Haskell met regularly with scientists from the Research Center for Radiation Medicine (RCRM). Except for the initial meeting that involved travel of Dr. Haskell to the Ukraine in February of 1987, the other meetings took place during scientific conferences and workshops and involved no expense under this subcontract. The meetings were used for discussion of issues relating to the accuracy of the EPR technique as well as design of intercomparisons for empirically testing the accuracy of the technique. The study involved one working visit by Dr. Sholom to the University of Utah in July of 1997. The purpose of this working visit was to assess the validity of earlier results obtained by this laboratory indicating potential changes to the sensitivity of enamel as a function of sample preparation method and proximity to carious portions of tooth enamel. Results of the study performed by Dr. Sholom during his visit to the University of Utah did not reveal significant problems associated with preparation technique or proximity to dental caries. The results have been presented at an international conference and were included in a previous quarterly report under this subcontract.

Two additional experimental studies performed by the University of Utah and the RCRM included analysis of samples exposed to ionizing radiation as part of a multilaboratory intercomparison conducted under the auspices of the IAEA. The results of this study were subsequently presented at an international conference and have recently been included in a previous progress report. Results by the University of Utah and the RCRM showed close internal agreement for the various doses applied and measured, however the slope of the dose response curve between the two laboratories varied significantly indicating the possibility of calibration differences. To address this problem and provide standardization and consistency between laboratories, the University of Utah has proposed a technique to circumvent this problem.

A second intercomparison was designed to examine the specific discrepancy between results of the University of Utah and the RCRM that appeared in the first intercomparison. This study involved irradiation of whole teeth by the IAEA and measurement of separate halves of teeth supplied by the University of Utah and by the RCRM. The results of this intercomparison have been reported by

the RCRM in their final report and reveal excellent agreement between the two laboratories. The results of both intercomparisons indicate that with proper methodologies and equipment, doses of radiation can be measured in artifactually irradiated teeth at the level of 100 mGy and below.

3.5 Dosimetry FISH:

Radiation-induced chromosome translocations in lymphocytic cells can be accurately quantitated by the fluorescence in situ hybridization (FISH) technique. Since translocations induced in stem cells usually survive and are transmitted to daughter cells, they presented a potential method for retrospective quantitation of radiation exposure. Lymphocyte samples could be readily obtained from subjects and their in vitro culture was already an established practice in Dr. Pilinskaya's laboratory in Kiev.

An initial visit to Dr. Pilinskaya's laboratory was made to determine the equipment and additional training required to prepare them to perform FISH analyses. Although being conducted under rather austere laboratory conditions, their lymphocyte culture procedures were yielding chromosome preparations adequate for FISH probing. An improved ultraviolet light source, dual band-pass filters and other minor components were needed to modify their microscope for adequate evaluation of fluorescence probed slides. These items, as well as the necessary fluorescent probes, were secured and hand carried to Kiev on a subsequent visit.

During this two-week visit, their microscope was upgraded and Dr. Dybskiy was trained in the application of the FISH method of probing for translocation identification. Stocks of the necessary reagents were formulated and properly adjusted. Slides were prepared using cells that had been previously cultured from 18 different donors and held in the freezer. All these samples yielded chromosome preparations with fluorescence intensity quite adequate for scoring.

A score sheet for recording cells scored and the various types of chromosome translocations encountered was prepared and its use discussed in detail. Extensive discussions were carried out on

the methods to be used for selecting cells for scoring to avoid bias and on the various scoring pitfalls to be avoided. A number of translocations identified on slides from one sample were jointly examined by Dr. Pilinskaya, Dr. Dybskiy and Dr. McFee, and their classifications were agreed upon. Kiev personnel were thus deemed adequately trained and equipped to conduct valid FISH evaluations.

Blood samples were obtained from 49 liquidators for whom adequate preliminary dose estimates and EPR measurements were available; these dose estimates ranged from <10 to >100 cGy. Lymphocyte cultures were performed and fluorescence whole-chromosome probes for chromosomes 1, 2 and 4 were applied. Translocations were scored in approximately 1000 metaphases from each donor and equivalent translocation rates per total genome were calculated. These translocation rates were used to prepare dose estimates for each liquidator. Since no in vitro dose-response curves had been established in the Kiev laboratory, published data from other laboratories were used to make the dose inference from translocation values.

FISH estimates of dose varied widely among individuals within EPR dose estimate groups. The mean doses determined for the groups did not show increases consistent with the presumed increasing dose received and the correlation between FISH and EPR dose estimates was very poor. While translocation induction theoretically should be a good measure of radiation dose, the wide variation in background levels among individuals (and perhaps some variation in individual sensitivity to induction) precluded their meaningful application. A paper dealing with the FISH-EPR dosimetry comparison in the 49 liquidators has been initially prepared by Dr. Pilinskaya and is currently being reviewed by her collaborators.

4. Administration

Administratively, the first year of the Contract began with establishing the infrastructure necessary to effectively support the goals of the program. The Columbia team was completed, and copiers, scanners, file cabinets and other equipment purchased by Columbia were delivered to the Chornobyl

office suite, and new Cyrillic software and graphic packages were installed.

As hardware systems became operational, the team focused on background support for the investigators. A sensitivity meeting lead by L. Zablotska and S. Kokoreva gave Columbia investigators insight into Belarussian/Ukrainian society prior to the first site visit. Literature searches, a library and translation and interpretation services provided investigators with necessary tools and allowing the scientific and administrative teams to develop a supportive working relationship. Core administrative activities included the institution of financial accounting systems, completion of the Utah Subcontract, development of filing systems, and coordination of team responsibilities.

As Year One ended, changes to the organization of the Contract were proposed to the NCI (November 23, 1998) and accepted (March 10, 1999). Dr. Howe's percent effort on the Contract was increased, a Russian speaking programmer was added, Drs. Matsushima and Fayter left Columbia, and were not replaced, current NCI consultants became NCI/Columbia consultants and the responsibility for Columbia team and consultants' travel was moved to the Contract. Also in March, Dr. Howe negotiated with Drs. Medvedovsky (radiobiology) and Worgul (radiobiology) for a reduction in their work effort. Further changes in the allocation of work effort for the Contract were foreseen and plans for discussions with NCI formulated. Additionally, in April of 1999 the responsibility for purchasing materials, supplies and equipment for delivery to the study sites was added to the Columbia Contract.

The administrative team worked with the University to develop the systems needed to support the additional responsibilities of the Contract. Agreements were reached with the Office of the Controller, Grants and Contracts, Purchasing, Accounts Payable, Restricted Funds and the Mailman School of Public Health to establish guidelines that would govern the procedures for handling the additional responsibilities.

Purchasing systems were then put in place and the backlog of supplies and equipment needed at the study sites was delivered. The next year's requests for supplies were received at the end of Year Two, evaluated by the Columbia team and consultants, sourced, priced and that information was provided to NCI at the November Tri-National Meeting in Bethesda. When approvals to purchase were reviewed the costs of the approved purchases were incorporated into the financial projections to the end of Contract Year Three and it became apparent that the Contract would require significant supplemental funding.

During discussions at the December 13, 1999 reverse site visit, S. Hodgson advised NCI that the next financial report (2706) would include purchasing estimates and indicate a serious projected deficit. This report was submitted in January of 2000 and the deficit was estimated at approximately one million dollars.

An administrative meeting at NCI on April 26, 2000 discussed possible ways to reduce the size of the projected deficit. Dr. Sohn (Columbia Office of Grants and Contracts) proposed that he attempt to procure the "off-site" Indirect Cost Recovery (ICR) rate for NCI directed purchases of material and equipment to be sent directly to Belarus and/or Ukraine. This rate of 24.9% was later negotiated by Dr. Sohn and went into effect on May 16, 2000. Columbia University efforts, particularly that of Dr. Sohn, resulted in a projected reduction in the deficit to under $875,000. The requirements for a Service Agreement with the University of Illinois and a Subcontract with the Research Clinical Institute of Radiation Medicine and Endocrinology in Minsk, Belarus were outlined. Both of these agreements were fully executed in the last quarter of Year 3 and they are currently in effect.

Columbia University and NCI subsequently revised the format for the financial report 2706 to include as expensed all projected salary items, to show approved purchases as encumbered items included in expensed dollar figures and to include a more detailed breakdown of items indicating the rate of indirect cost recovery charged to individual line items. It is anticipated that these changes will more accurately present both current expenditures and projected costs.

In August 2000 supplemental funds of approximately $975,000 were added to the Contract to provide for purchasing of material, supplies and equipment; the Illinois Service Agreement, the Belarussian Subcontract and the purchase of equipment for the leukemia study. Purchase orders for remaining supplies were issued and shipments arranged.

Throughout the third year of the Contract the changing needs of the project were addressed and plans were made for future modifications. Negotiations between Columbia and NCI for changes in the work effort of the Contract during Option Year 1 were finalized in September of 2000 and Option Year 1 was awarded.

5. Training

Columbia is responsible for providing the logistics for individuals from Belarus and Ukraine who come to the United States or elsewhere for training purposes. In some cases Columbia has also contributed directly to the training of such individuals. Table 1 provides a summary of individuals who have been supported for training under the contract, and also gives the places where such training has been carried out.

TABLE 1

SUMMARY OF BELARUSSIAN AND UKRAINIAN SCIENTISTS TRAINED UNDER THE AUSPICES OF THE CONTRACT

NAME	AREA OF TRAINING	MONTH/YEAR	LOCATION
Buglova, Elena	Epidemiology Epidemiology Data Collection	Aug. 1999 Sept. 1999 Aug./Sept. 1999	Univ. of Illinois, Chicago Columbia Univ., NY Westat, Rockville, MD
Golovneva, Alla	Epidemiology SAS Data Collection Epi/Data Collection	June-July 2000 July 2000 July, 2000 July-Aug. 2000	Johns Hopkins, MD IMS/Rockville, MD Westat, Rockville, MD Columbia Univ., NY
Krioutchkov, Victor	Record Linkage	Feb-March 1999	NCI, Rockville, MD
Lesnikova, Nadia	SAS/Data Management Epi/Data Collection	Aug. 1999 Sept., 1999	Westat, Rockville, MD Columbia Univ., NY
Sholom, Sergei	EPR Dosimetry EPR Dosimetry	July 1998 July 2000	University of Utah, UT Rocky Mountain Conference Analytical Dose Estimation, CO

6. Training Human Subjects Issues

Under the contract renewal, Columbia has been given the task of ensuring that all Columbia investigators and consultants have received the appropriate training in human subjects issues, and also providing such training for our collaborating colleagues in Belarus and Ukraine. Since the present report is the first deliverable during the time period of the renewed contract, this section briefly details the proposed plans for this task.

All Columbia investigators and consultants have been requested to complete the appropriate training which each of their respective institutes provides by the end of 2000. For example, Columbia provides such a course, with a corresponding test and plans are in place for Columbia investigators to take this course and test. Consultants at other institutions have been asked to investigate the current position in their own institutions and, if similar courses exist, to take them by the end of the year. An alternative is to take the website course and test sponsored by NIH.

With regard to the Belarussians and Ukrainians, the situation is more complex. At the moment, a one-day course based on the Columbia model is being planned for Kiev in early February, with a similar course planned for Minsk during the same week. It is hoped that the course will be taught by Dr. Richard Sohn, Director of the Office of Grants and Contracts at Columbia University, who is responsible for the Columbia course. In order to illustrate the type of material which might be presented in Kiev and Minsk, Appendix 6 contains a sample of the slide material used in the current Columbia course. This, of course, would have to be translated into Russian for the Belarussian and Ukrainian scientists participating and care will have to be taken to ensure that Belarussian and Ukrainian sensibilities are not offended since the investigators concerned have many years of experience in conducting studies amongst human subjects.

APPENDIX 1

Columbia Staff, Collaborators and Consultants Involved During the First Three Years of the Contract

Columbia Staff:

G.R. Howe (epidemiology), Principal Investigator

J.D. Burch (epidemiology)

D.J. Fink (clinical laboratory management)

C.R. Geard (biological dosimetry)

E. Greenebaum (cytology/pathology)

J. Fayter (ultrasonography)

D.F. Heitjan (biostatistics)

A. Matsushima (hematology)

R.J. McConnell (endocrinology)

C. Medvedovsky (radiobiology)

R.F. Reiss (hematology)

B. Worgul (radiobiology)

S. Hodgson (administration)

D. Illian (administration)

S. Kokoreva (administration)

L. Zablotska (administration)

E. Haskell (dosimetry)

T. Straume (dosimetry)

Consultants:

A. Brill (ultrasonography)

S. Finch (hematology)

G. Littlefield (biodosimetry)

A. McFee (biodosimetry)

H. Mitchell (data management)

J. Robbins (endocrinology)

APPENDIX 2

McConnell's Abstracts

PROGRESS IN THE BELARUS-USA COHORT STUDY OF THYROID AND PARATHYROID DISEASE FOLLOWING THE CHERNOBYL ACCIDENT

Polyanskaya O, Buglova E, Cherstvoy E, Danilova L, Demidchik Y, Drozd V, Kuvshinnikov A, Lesnikova, N, Litvinova N, Minenko V, Mrotchek A, Petrenko S, Rzheutski V, Stezhko V, Beebe GW, Brill AB, McConnell R, Robbins J.
Clinical Research Institute of Radiation Medicine and Endocrinology, Ministry of Health, Minsk, Belarus; National Cancer Institute, National Institute of Health, Rockville, MD, USA; Columbia University, New York, NY, USA.

The risk of thyroid cancer has been established for exposure to external radiation therapy and to the atomic bomb, but the risk from internal radiation by radioiodine remains undefined despite the widespread use of I-131 in diagnosis and therapy. External radiation is also followed by increased incidence of benign thyroid nodules, autoimmune thyroiditis and hyperparathyroidism. Radiation during childhood clearly poses the greatest risk. Fallout from the Chernobyl accident has greatly increased thyroid cancer and provides a unique opportunity to quantify the risk from radioiodine. The most reliable way to achieve this goal is by the study of a well-defined cohort of exposed individuals. A statistical power analysis indicates that a cohort of 15000 might be sufficient. The Belarus-USA Project screens individuals under age 18 years at the time of the accident (26 April 1986) who had direct radiation measurement of the thyroid in May and June 1986. Since 1 January 1997, the project has enrolled all of 8400 children with a preliminary thyroid dose estimate of $\geq$1 Gy, 3500 randomly selected from a list of 11000 with a dose of 0.3 to <1 Gy, 3500 selected from 19700 with a dose of < 0.3 Gy. Subjects will be examined biennially at fixed sites and by mobile teams for up to 30 years after the accident. Procedures include thyroid palpation and echography, and assay of serum TSH, anti TPO and ionized calcium, with backup procedures including serum free T4; anti TG and PTH. Initially, serum TG and urine iodine are also assayed, and a detailed interview covers location and activities in 1986, source and consumption of milk and other foods, iodine prophylaxis and other matters needed for radiation dose reconstruction. Thyroid nodules are investigated by aspiration biopsy and clinically indicated surgical excision. Rigid quality control procedures include expert review of cytological and histological specimens and laboratory results. By 1 March 1999, 3649 subjects had been screened, among whom there were 134 nodular goiters (3.7%). Of the nodular goiters, 80% were solitary. There were 41 thyroid cancers (1.1%), 28 previously diagnosed and 13 diagnosed for the first time. All were papillary cancers. Thyroid volume by ultrasound was measured in 3357 intact glands. Compared to an age-matched, unexposed Belarus population, 687 (20%) were above normal, 140 (4.2%) greater than 150% of normal, and 28 (0.8%) greater than 200% of normal. Individual dose reconstruction in the cohort will provide an estimate of thyroid cancer risk from radioiodine.

PREVALENCE OF THYROID ANTIBODIES IN THE BELARUS-USA STUDY OF THYROID CANCER AND OTHER THYROID DISEASES FOLLOWING THE CHERNOBYL ACCIDENT.

V. Ostapenko, S. Petrenko, O. Polyanskaya, V. Rzheutski, N. Litvinova, N. Lesnikova, V. Drozd, L. Danilova, V.Stezhko, G. Beebe, A.. Brill, D. Fink, E. Greenebaum, G. Howe, R. McConnell, I. Masnyk, J. Robbins Clinical Research Institute of Radiation Medicine and Endocrinology, Ministry of Health, Belarus; National Cancer Institute, National Institute of Health, Rockville, MD, USA; Columbia University, N Y, NY, USA.

An increase in thyroid nodules and cancer followed the release of radioiodine by the Chernobyl accident on 26 April 1986. Less thoroughly evaluated has been the prevalence of thyroid autoimmunity, even though external irradiation is recognized to increase the incidence of autoimmune thyroiditis. The Belarus-USA Study was established to quantitate the risk of thyroid disease in a well-defined cohort of individuals under age 18 years at the time of the accident (ATA) who had direct thyroid radiation measurements. The cohort consists of 8400 children with a thyroid dose estimate of $\geq$ 1 Gy, 3500 with a dose of 0.3 to < 1 Gy, and 3500 with a dose of < 0.3 Gy. Subjects are examined at least biennially by thyroid palpation and ultrasound (US) and assay of serum for thyroid antibodies, TSH, free T4, and thyroglobulin. By 1 January 2000, 5965 cohort members were screened at least once, among whom 2638 had palpable thyroid glands and also thyroid antibody assay. AntiTPO or antiTG, or both, was elevated in 167 (6.3%), of whom 111 were female and 56 male (F/M=2/1). In 80 (3.0%) only antiTPO was elevated, in 44 (1.7%) only antiTG, and in 43 (1.6%) both. The highest prevalence (13.1%) was in females aged 15-18 years ATA. Thyroid US volume was available in 2669 cohort members who also had antibody assay. Compared to an age-matched, unexposed Belarussian population, 423 (15.8%) had volumes above normal. Either antibody was elevated in 6.2% of subjects with normal volumes, 8.2% of those up to 150% of normal, and 12.2% of those 150-200% of normal. Either antibody was elevated in 5 of 27 (18.5%) cancers, 11 of 179 (6.1%) solitary nodules, and 8 of 77 (10.4%) multinodular goiters. In females aged 15–18 years ATA with nodular disease, antibodies were positive in 26.9%. The eventual goal of this part of the cohort study is to correlate individually reconstructed thyroid radiation doses with the occurrence of autoimmune thyroiditis.

SCREENING OF THYROID STATUS AFTER THE CHORNOBYL ACCIDENT

Tronko M., Bogdanova T., Epshtein O., Oliynyk V., Tereshchenko V., Likhtaryov I., Kairo I., Beebe G., Bouville A., Brill A., Fink D., Howe G., Masnyk I., McConnell R., Robbins J. Greenebaum E.

Institute of Endocrinology and Metabolism, AMS Ukraine, Kyiv, Ukraine;
Scientific Center of Radiation Medicine, AMS Ukraine, Kyiv Ukraine;
National Cancer Institute, National Institute of Health, Rocksville, MD, U.S.A.;
Columbia University, New York, NY, U.S.A.

To answer the question of the influence of radioactive iodine on thyroid status after the Chornobyl accident long-term large-scale studies are performed in the framework of the Ukraine-US Thyroid Project. According to the Project protocol, screening involves persons aged 0 to 18 years at the time of the accident, who were living then in those areas of Ukraine that have been the most contaminated by radioactive iodine (9 districts of Kyiv, Chernihiv, Zhytomyr regions).
Out of these persons, a cohort of 20 000 subjects has been established, in whom direct measurements of thyroid activity of I-131 have been made immediately after the accident. Among them 10000 with a dose of 1 Gy and more; 5 000 with a dose 0.3 - 1 Gy; 5 000 with a dose less than 0.3 Gy. Observation is planned for up to 30 years, with a frequency of one examination every two years. For convenience of screening subjects, examinations are performed mainly by mobile medical teams at places of residence of study subjects, and by a stationary team at the Institute of Endocrinology in Kyiv. Screening includes thyroid palpation and echography; serum TSH assay; anti-TPO, ionized calcium tests, as well as ancillary procedures which include serum free T4 assay; anti-TG, PTH, urinary iodine tests. In case of thyroid nodules, FNAB of nodules is performed, with cytologic study of aspirated material. Quality control includes expert verification of cytologic, histological, and laboratory data. As of 18.04.2000, 7 141 persons have been examined. Thyroid nodules have been found in 100 persons, 24 of whom have undergone surgery. In 14 patients (1 child aged 14, 3 adolescents aged 15-16, and 10 young adults aged 21-30 years) papillary thyroid carcinoma, and in 10 benign pathology (5 follicular adenomas, 2 multinodular adenomatous goiters, 1 nodular goiter, 1 degenerative fibrotic nodule, and 1 Graves' disease) have been diagnosed. In 11 out of 14 cases of thyroid cancer thyroid dose exceeded 1 Gy. Sex ratio (F:M) for the thyroid cancer cases was 9:5.

APPENDIX 3

Criteria for Performing Fine Needle Aspiration (FNA)

CRITERIA FOR PERFORMING FNA

1. Any thyroid nodule or focal lesion that is 10mm or greater in largest diameter and is detected either by palpation or sonography.

2. A thyroid nodule or focal lesion smaller than 10mm that is not a pure cyst and that has any of the following ultrasonic or palpable features that are suspicious for malignancy:
   Unclear or irregular borders.
   Extension through thyroid capsule.
   Heterogeneous or hypoechoic ultrasonic density.
   Stippled (or punctate) calcification.
   Increasing size during followup.
   Abnormal lymph nodes of uncertain etiology.

3. Diffusely abnormal thyroid accompanied by unexplained cervical lymphadenopathy. In this case, FNA will be done on one or more lymph nodes, and the thyroid may also be biopsied.

4. In the case of indeterminate cytology, FNA will be repeated up to 3 times within the period of one year.

APPENDIX 4

Criteria for Diagnosing Autoimmune Thyroiditis (AIT)

CRITERIA FOR DIAGNOSING AUTOIMMUNE THYROIDITIS (AIT)

Main criteria

- Histopathology (diffuse or focal)
- Cytopathology (lymphocytes plus oxyphils)
- AntiTPO ≥ 500 at least twice
- Anti TG ≥ 1000 at least twice

Additional criteria

- AntiTPO > reference range and <500
- AntiTG > reference range and < 1000
- Ultrasound (hypoechoic, heterogeneous)
- Palpation (firm, irregular)
- TSH > reference range
- Cytopathology (lymphocytes only)

Diagnosis = AIT

High probability

- One or more of the main criteria

Moderate probability

- AntiTPO or antiTG > reference range and < 500 or 1000 plus at least 2 other additional criteria
- AntiTPO and antiTG within reference range plus at least 3 additional criteria

APPENDIX 5

Methods for Clinical Management of Non-operated Thyroid Nodules

THYROXINE TREATMENT OF PATIENTS WITH THYROID NODULES NOT SENT TO SURGERY:

(1). Patients excluded for hyperthyroidism, unstable cardiovascular disease, and other recognized contraindications to thyroid hormone therapy

(2). No age exclusion

(3). Treat nodules larger than 5 mm in diameter, with the exception of simple cysts

(4). Beginning dose of 2 mcg/kg/day with adjustment after 3 months to an optimal TSH level of 0.1-0.2 mU/L, then monitor at 6-month intervals

(5). Therapy continued indefinitely or until shown to be of no value in causing the nodule to decrease in size or preventing the development of new nodules.